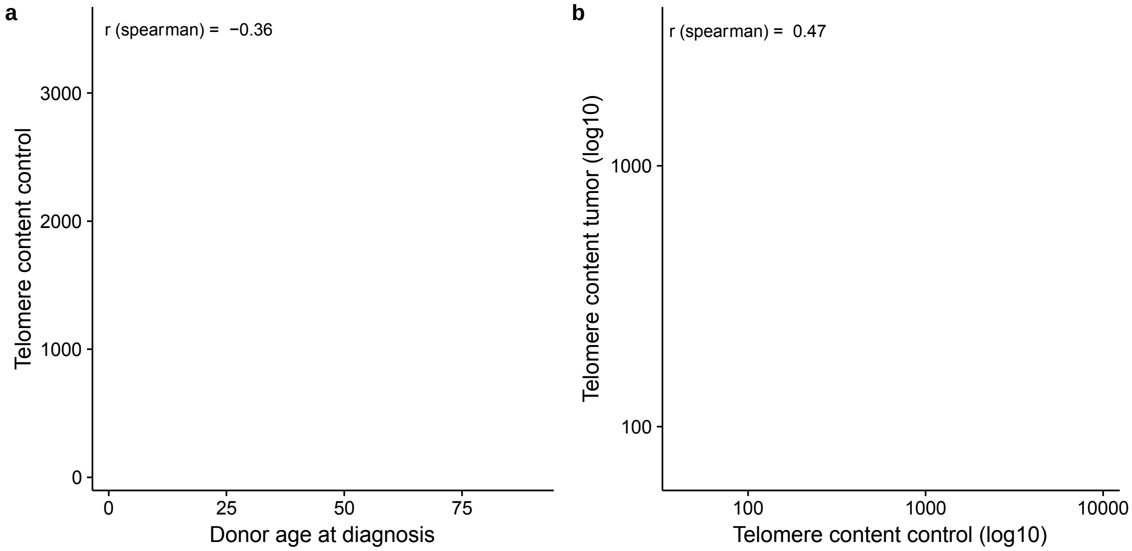
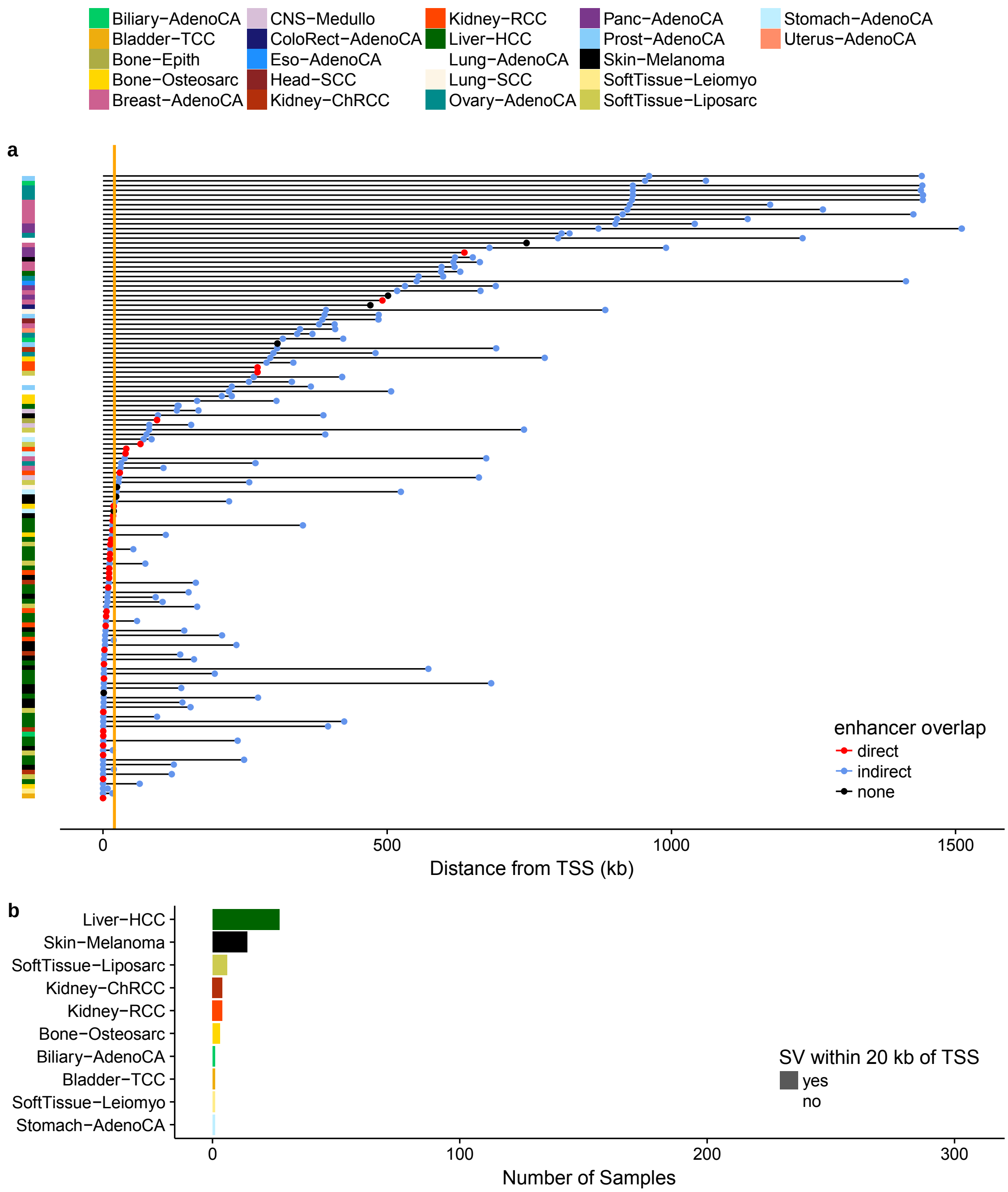
Genomic footprints of activated telomere maintenance mechanisms in cancer

Supplementary Information

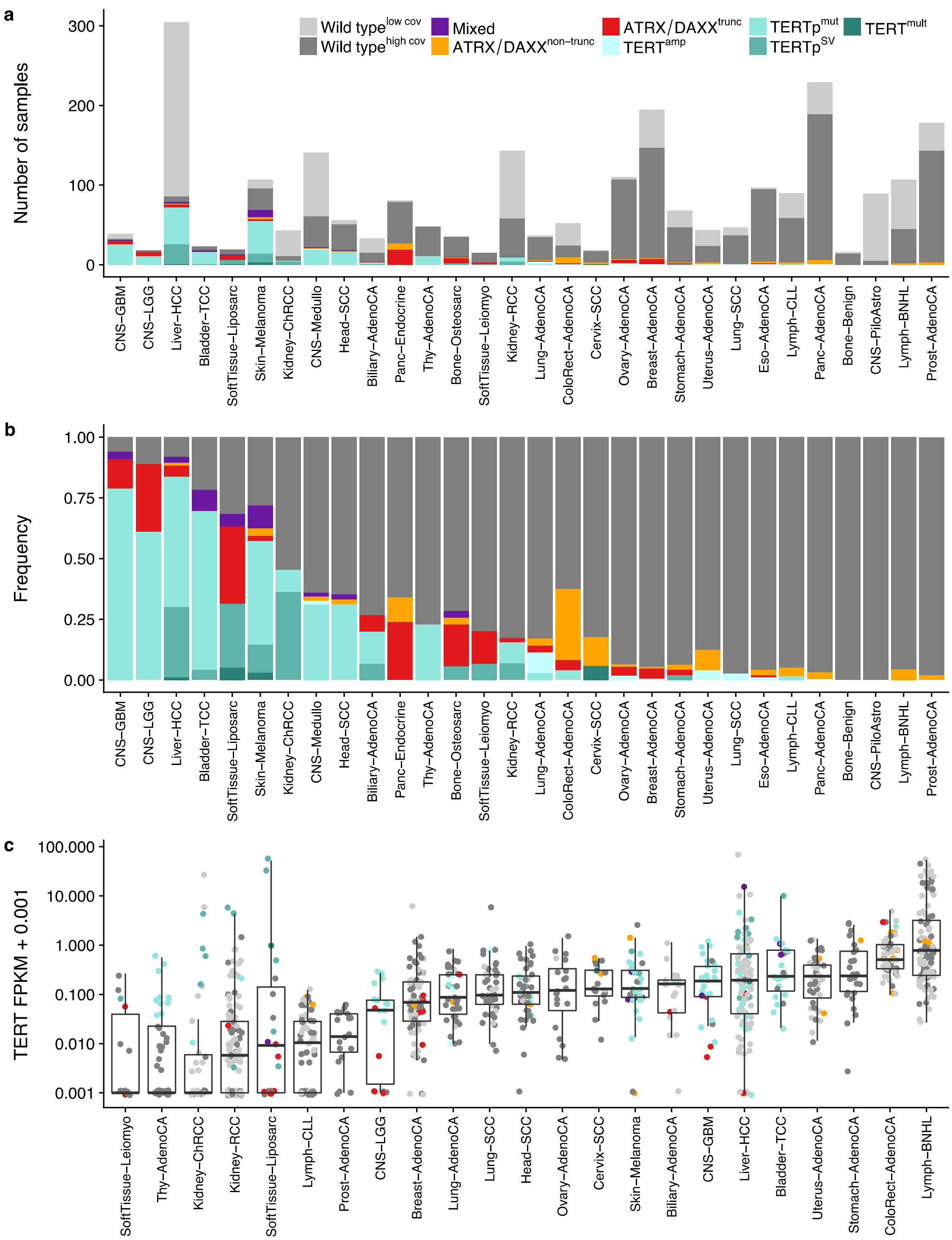
Sieverling *et al.*



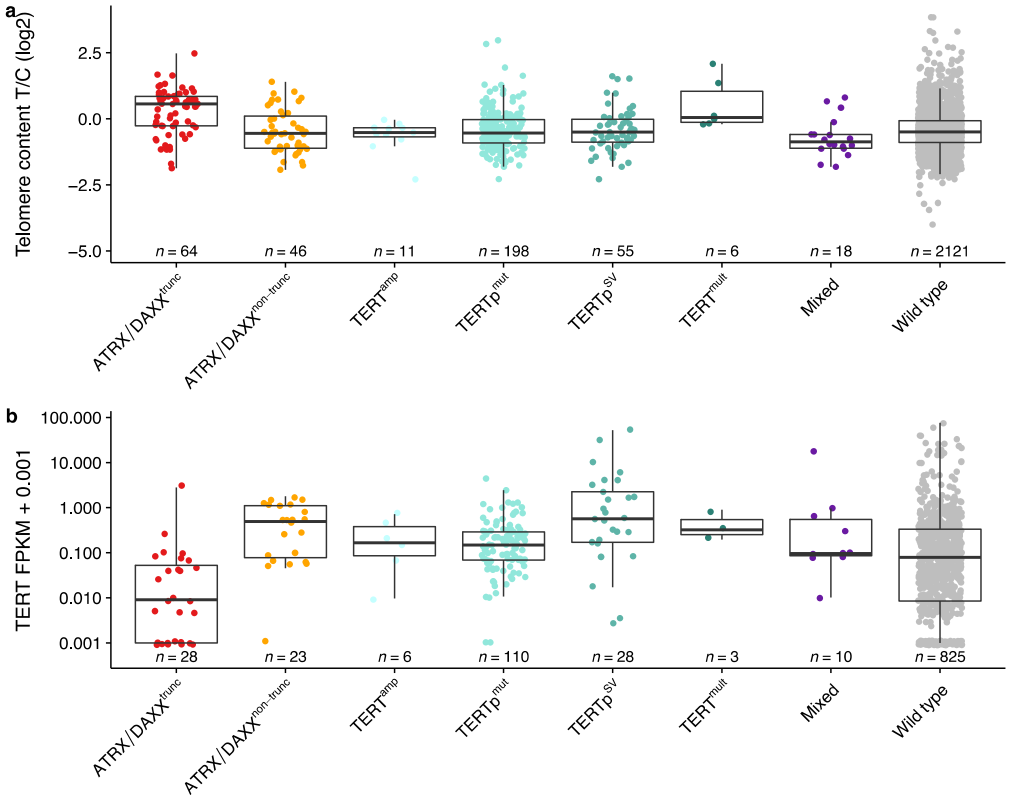
Supplementary Figure 1: Influences on telomere content. (a) Correlation of control telomere content and the patient age at diagnosis. (b) Correlation of telomere content in the tumor and the control sample.



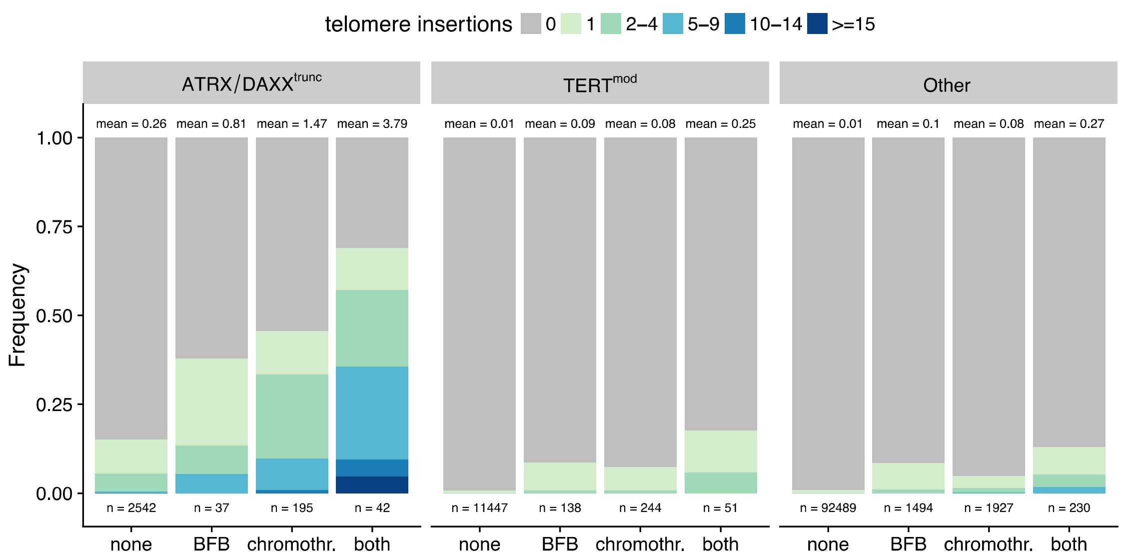
Supplementary Figure 2: Structural variations upstream of *TERT*. (a) Distance of structural variations (SVs) up to 1 mb upstream of the *TERT* transcription start site (TSS). For each tumor sample, only the SV closest to the TSS is shown. Direct overlaps of juxtaposed positions with dbSUPER enhancer regions are indicated in red. dbSUPER enhancers upstream of the SV are shown in blue, where the first point of each line is the position of the SV and the second point is the rearranged enhancer position. All tumor samples with SVs within 20 kb of the *TERT* TSS (orange line) were considered as TERT^{mod} for the further analysis. (b) Number of samples per tumor type with and without an SV within 20 kb of the *TERT* TSS. Only tumor types with at least one affected sample are shown.



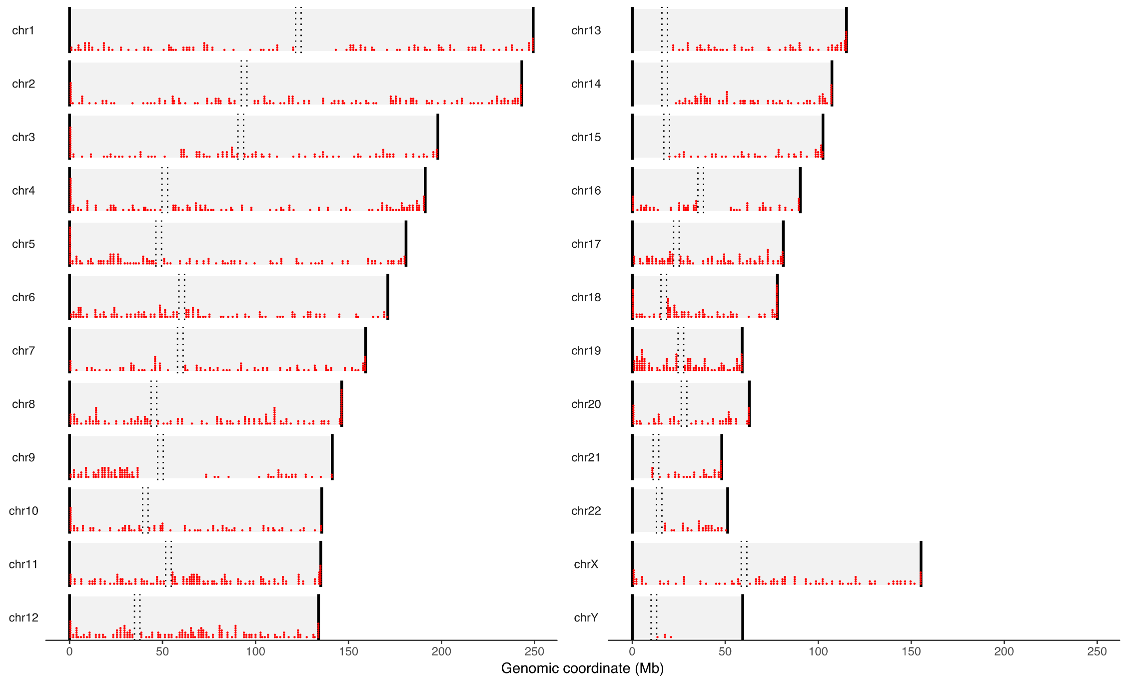
Supplementary Figure 3: TMM-associated mutations and *TERT* expression in different tumor types. (a) Number of samples with TMM-associated mutations. Wild type tumors (i.e. tumors without TERT^{mod} or mutation in *ATRX* or *DAXX*) were divided into those with a coverage of at least 10 reads at *TERT* promoter positions chr5:1,295,228 and chr5:1,295,250 (Wild type$^{high\ cov}$) and those without (Wild type$^{low\ cov}$). The tumor types are sorted by the frequency of ATRX/DAXX^{trunc} and TERT^{mod} samples. (b) Frequency of TMM-associated mutations. Wild type tumors with low coverage at the *TERT* promoter were excluded. (c) *TERT* expression in different tumor types. The tumor types are sorted by increasing median *TERT* expression. The center line of the boxplot is the median, the bounds of the box represent the first and third quartiles, the upper and lower whiskers extend from the hinge to the largest or smallest value, respectively, no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles).



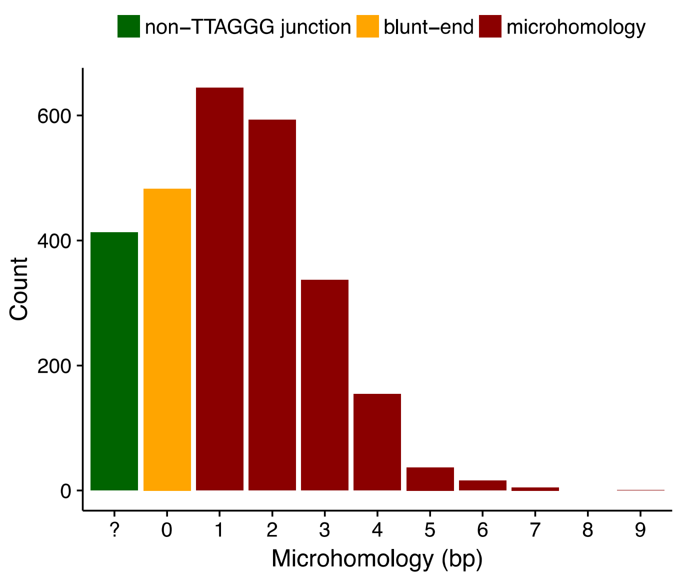
Supplementary Figure 4: Telomere content and *TERT* expression of tumor samples with different TMM-associated mutations. (a) Telomere content tumor/control log2 ratios. (b) *TERT* expression in FPKMs. The center line of the boxplot is the median, the bounds of the box represent the first and third quartiles, the upper and lower whiskers extend from the hinge to the largest or smallest value, respectively, no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles).



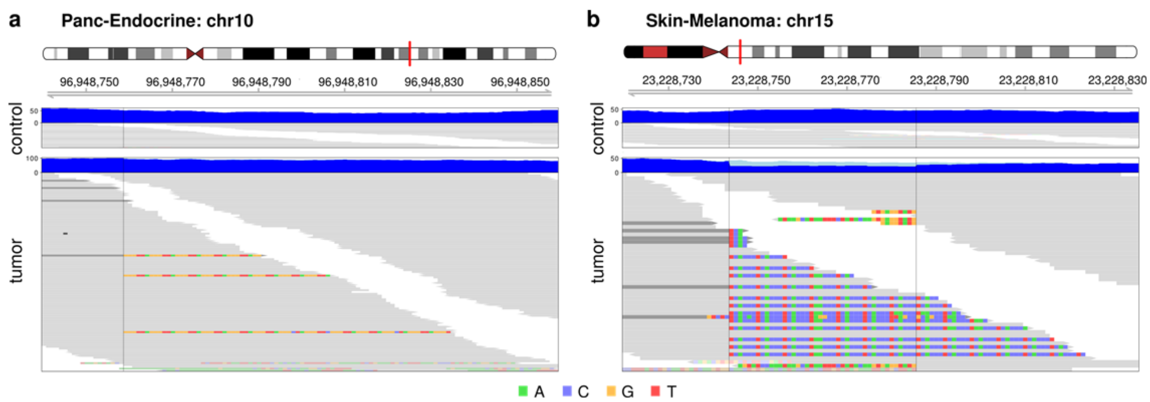
Supplementary Figure 5: Co-occurrence of telomere insertions, breakage-fusion-bridge (BFB) cycles and chromothripsis on the same chromosome arm. Autosomal chromosome arms of patients with different TMM-associated mutations were divided into those with indication of BFB cycles, chromothripsis, both or none of these complex structural abnormalities. The frequency of telomere insertion counts is shown for each of the classes. The total number of chromosome arms falling into each category (n) and the mean number of telomere insertions is indicated.



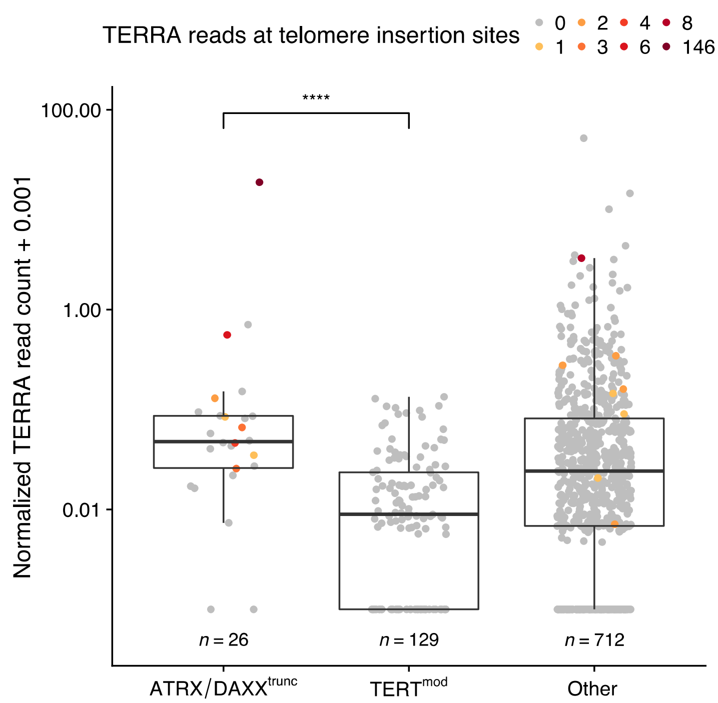
Supplementary Figure 6: Chromosomal positions of telomere insertions. Telomere insertions of all patients are shown.



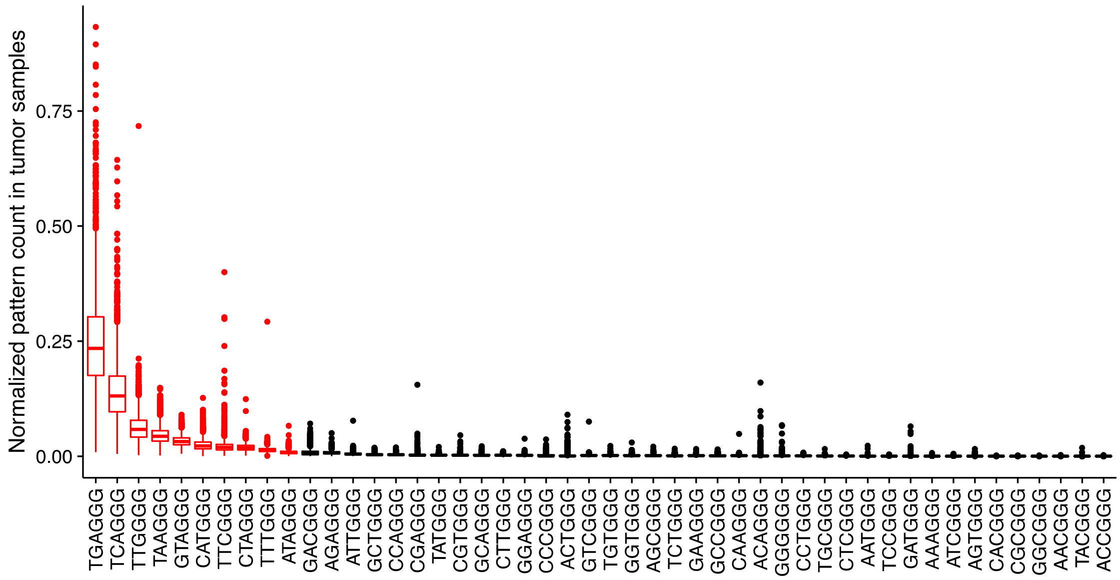
Supplementary Figure 7: Patterns of microhomology at telomere insertions. The number of homologous bases between the canonical TTAGGG telomere repeat and the human reference genome at telomere insertions is shown on the x-axis. The number of telomere insertions with a pattern of TTAGGG microhomology (red), blunt-end DNA joining (yellow) or without TTAGGG repeats at the junction site (green) are shown on the y-axis.



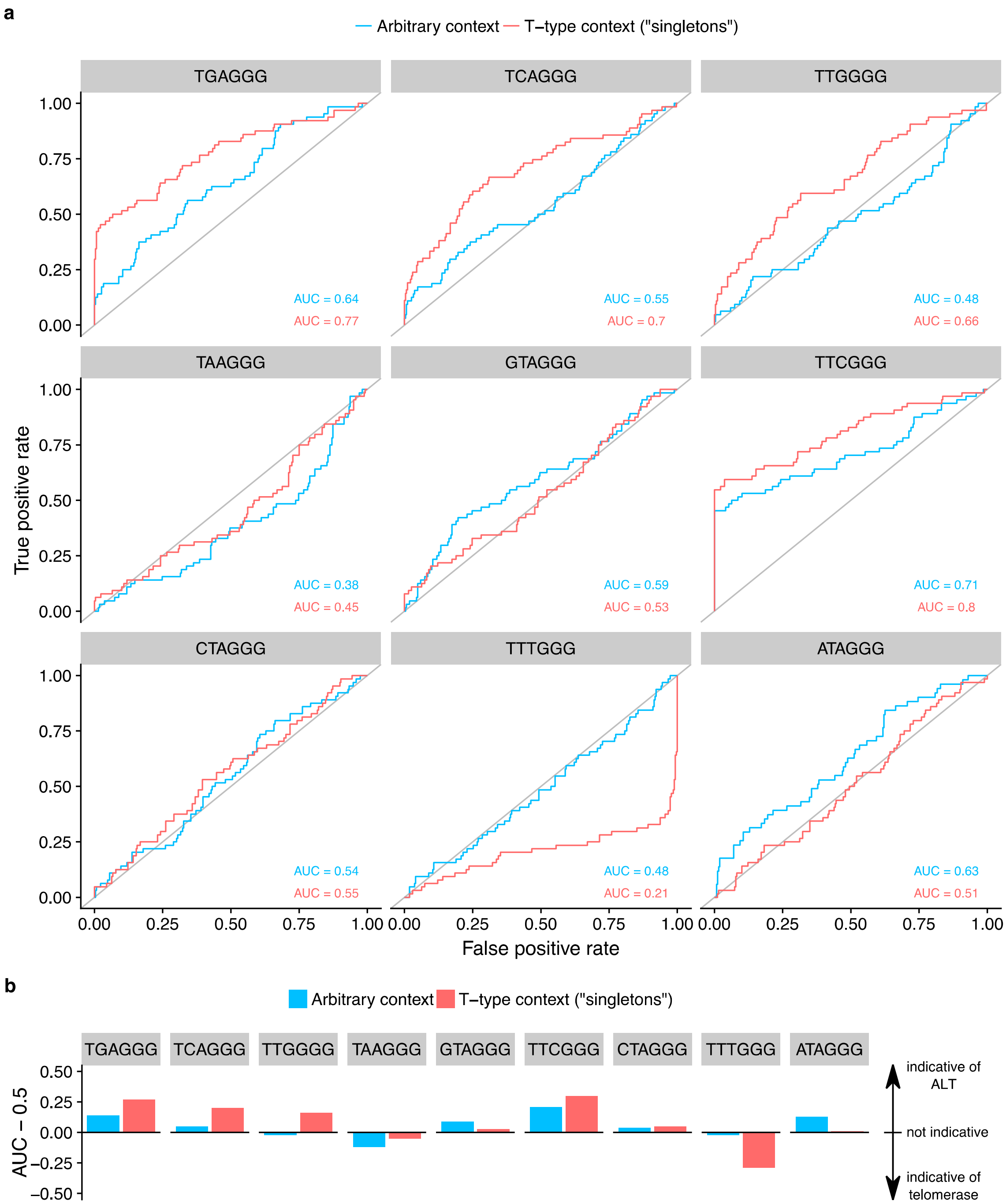
Supplementary Figure 8: Examples of one-sided telomere insertions without annotated accompanying structural variations. (a) Subclonal telomere insertion in pancreatic endocrine tumor sample SP102547 (copy number at position = 2; tumor purity = 0.87, as determined by copy number calls). Blue tracks show the sequencing coverage; light blue represents clipped sequences. Individual reads are grey and clipped bases are colored. Non-telomeric clipped bases are transparent. Dark grey reads represent the non-telomeric end of a discordant read pair. (b) Unannotated structural variation (position 23,228,785; opaque non-telomeric clipped reads) opposite of a telomere insertion (position 23,228,744) in melanoma sample SP82836.



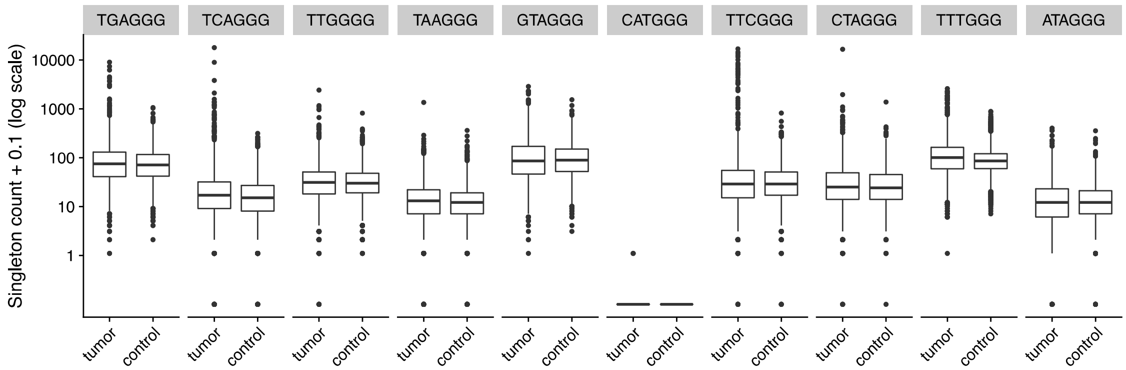
Supplementary Figure 9: TERRA expression in tumor samples with different TMM-associated mutations. The samples are colored by the number of TERRA reads mapping to telomere insertions sites. The center line of the boxplot is the median, the bounds of the box represent the first and third quartiles, the upper and lower whiskers extend from the hinge to the largest or smallest value, respectively, no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles). ****$p < 0.0001$, Wilcoxon rank-sum test.



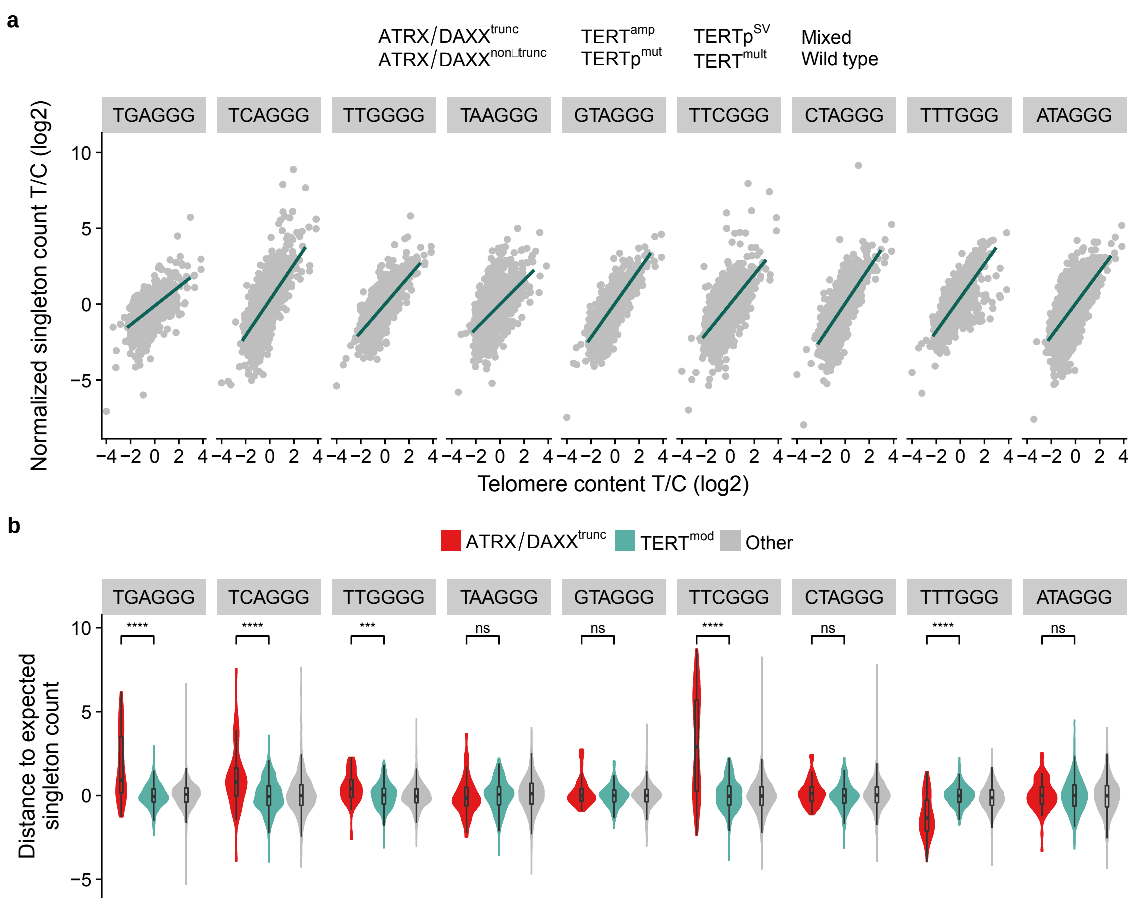
Supplementary Figure 10: Frequency of TVRs in arbitrary context. The mean pattern counts per telomere read are shown for all tumor samples. TVRs shown in red were investigated further regarding sequence context. The center line of the boxplot is the median, the bounds of the box represent the first and third quartiles, the upper and lower whiskers extend from the hinge to the largest or smallest value, respectively, no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles).



Supplementary Figure 11: The neighborhood of TVRs is indicative of the telomere maintenance mechanism. (a) Receiver operating characteristic for the classification of samples with ALT-associated mutations from telomere variant repeats. Red: no specific sequence context required. Blue: singletons ($(TTAGGG)_3$-NNNGGG-$(TTAGGG)_3$). (b) Area under the curve (AUC) for the classification of ALT using repeat type counts in different sequence context.

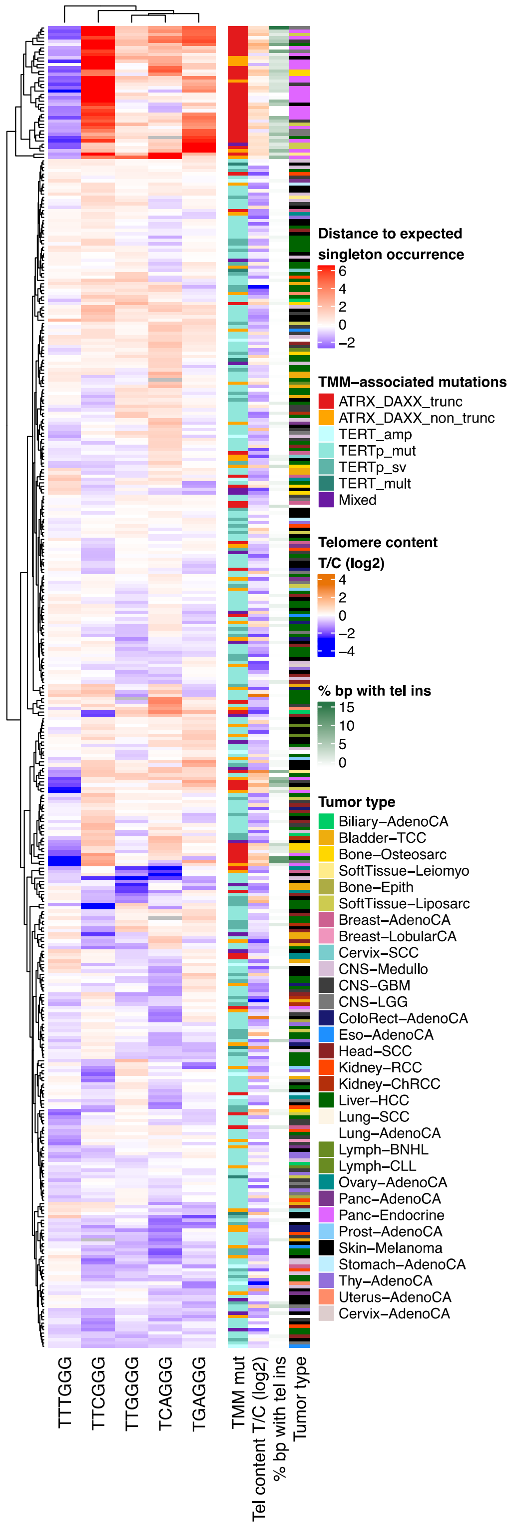


Supplementary Figure 12: Raw counts of singleton TVRs across all samples. Singleton counts are shown in log scale for all tumor and control samples. A pseudocount of 0.1 was added. The center line of the boxplot is the median, the bounds of the box represent the first and third quartiles, the upper and lower whiskers extend from the hinge to the largest or smallest value, respectively, no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles).

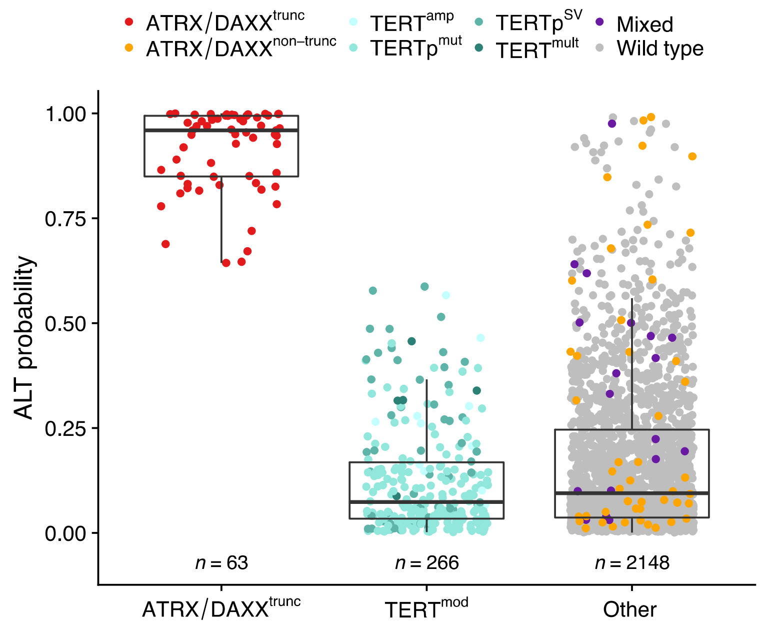


Supplementary Figure 13: Singleton TVRs. (a) Pattern count tumor/control log2 ratios of all patients plotted against telomere content tumor/control log2 ratios for analyzed singletons. The regression line through the TERT^{mod} samples is shown in green and is defined as the expected pattern count. (b) Distance to the expected singleton repeat count in ATRX/DAXX^{trunc} and TERT^{mod} samples. The center line of the boxplot is the median, the bounds of the box represent the first and third quartiles, the upper and lower whiskers extend from the hinge to the largest or smallest value, respectively, no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles). ****$p < 0.0001$; ***$p < 0.001$; ns = not significant, Wilcoxon rank-sum tests after Bonferroni correction.

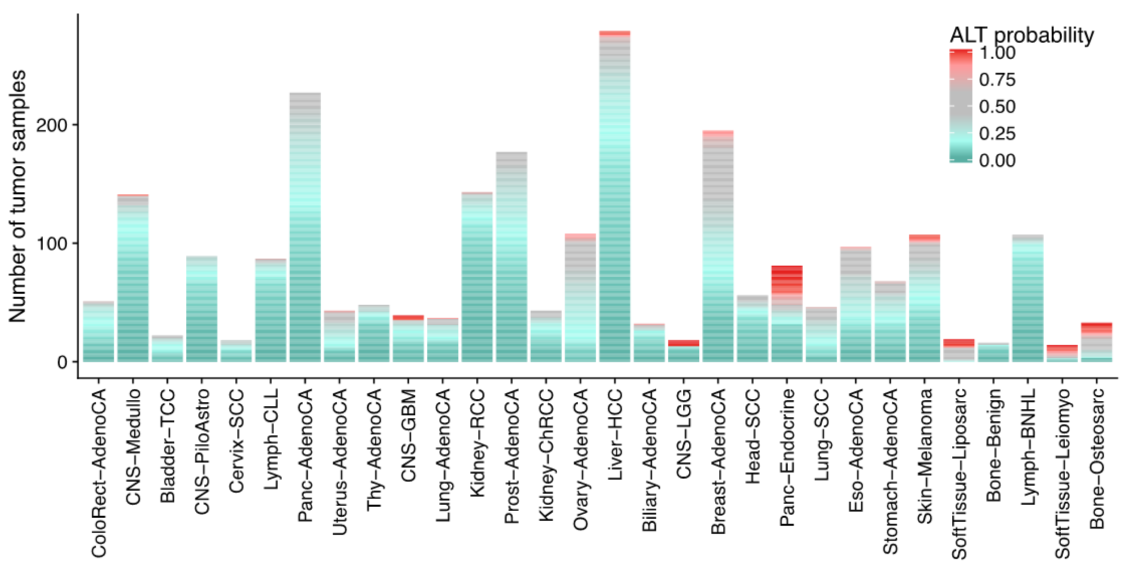
Supplementary Figure 14: Correlation of singleton TVRs in ATRX/DAXX^{trunc} samples. The Spearman correlation coefficients for the occurrence of the significantly enriched/depleted singleton TVRs in ATRX/DAXX^{trunc} samples is shown.



Supplementary Figure 15: Clustering by singleton TVR occurrences. The heatmap depicts the difference of observed singleton occurrence to the expected occurrence (columns) for tumor samples with TERT^{mod} and/or mutations in *ATRX* or *DAXX* (rows). The TMM-associated mutations, telomere content tumor/control (log2), percent of breakpoints with telomere insertion and tumor type are annotated.



Supplementary Figure 16: ALT probability of tumor samples with different TMM-associated mutations. The ALT probability was derived from a random forest classifier trained to distinguish ATRX/DAXX^{trunc} from TERT^{mod} samples based on the following features: telomere content tumor/control log2 ratio, number of telomere insertions, number of break points and the distance of TGAGGG, TCAGGG, TTGGGG, TTCGGG and TTTGGG singletons to their expected occurrence. The classifier was only applied to samples without missing data. The center line of the boxplot is the median, the bounds of the box represent the first and third quartiles, the upper and lower whiskers extend from the hinge to the largest or smallest value, respectively, no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles).



Supplementary Figure 17: Prediction of ALT probability in different tumor types. For each tumor sample, the ALT probability predicted by a random forest classifier is shown. The tumor types are ordered by mean telomere content tumor/control log2 ratio (from left to right). Cohorts with sample sizes below 15 are not shown.

Supplementary Table 1: Mutated genes significantly associated with telomere insertions. The genes were obtained from correlation analysis of telomere insertions and mutations of genes from the TelNet database. q-values were calculated with Wilcoxon rank-sum tests with Benjamini-Hochberg correction.

Gene	**q-value**	**Association with telomeres/telomere maintenance**
TP53	1.9×10^{-42}	Co-mutations of the tumor suppressor gene *TP53* with *ATRX* and *H3F3A* were found in pediatric glioblastoma[1]. p53 was also found to inhibit telomerase[2], thus truncated p53 was associated with high levels of TERT[3].
ATRX / DAXX	2.6×10^{-6} / 0.019	The death domain-associated protein DAXX and the chromatin remodeling factor ATRX (a-thalassemia/mental retardation syndrome protein) are specifically associated with the H3.3 deposition machinery. The loss of function of ATRX and/or DAXX correlates with the ALT phenotype[4-7].
PLCB2	7.8×10^{-4}	The yeast homologue of PLCB2, PLC1, was found in a TLC1 knock out study[8].
MEN1	0.017	The tumor suppressor menin, encoded by *MEN1*, was reported to negatively regulate telomerase by binding to the *TERT* promotor[9], while siRNA-based inhibition of *MEN1* does not lead to the up-regulation of hTERT mRNA expression[10]. A germline mutation in *MEN1* predisposed to developing pancreatic neuroendocrine tumors. In a study of 50 patient samples, 6% of this tumor entity show loss of ATRX and/or DAXX expression and activation of ALT[6]. Also, it was found to inversely be associated with telomere length[11]. In agreement with this, mutations in MEN1 were associated with increased telomere length in pancreatic endocrine neoplasms[12].
TSSC4	0.017	TSSC4 was found in close proximity to RAP1 by a PCA/BiFC assay[13].
RB1	0.018	The tumor suppressor RB1 was predicted to be potentially involved in telomere maintenance by Lovejoy *et al.* because it is part of the DNA damage response machinery[5]. Gonzalez-Vasconcellos *et al.* showed that both telomeric chromatin compaction and telomeric repeat-containing containing RNA (TERRA) transcription are dependent on RB1 expression[14].
ABCC8	0.04	The yeast homologue of ABCC8, YOR1, was found in two independent deletions screens in *S. cerevisiae*[8,15].

Supplementary Table 2: Prevalence of ALT-like telomere composition in different tumor types. Tumor samples were considered to have an ALT-like telomere composition if the difference of the TGAGGG, TCAGGG, TTGGGG or TTCGGG singleton occurrence to the expected occurrence was larger than 2.5, or if the difference of the TTTGGG occurrence in t-type context to the expected occurrence was lower than -2.

Tumor type	**n/N**	**%**
SoftTissue-Leiomyo	9/15	60
Panc-Endocrine	34/81	42
SoftTissue-Liposarc	7/19	37
Bone-Osteosarc	10/35	29
CNS-LGG	5/18	28
CNS-GBM	5/39	13
Bone-Epith	1/10	10
Kidney-ChRCC	3/43	7
Skin-Melanoma	8/107	7
Bone-Benign	1/16	6
Liver-HCC	14/305	5
Uterus-AdenoCA	2/44	5
CNS-Medullo	6/141	4
ColoRect-AdenoCA	2/52	4
Biliary-AdenoCA	1/33	3
Kidney-RCC	4/143	3
Eso-AdenoCA	2/97	2
Lymph-BNHL	2/107	2
Lymph-CLL	2/90	2
Ovary-AdenoCA	2/110	2
Breast-AdenoCA	1/195	1
Panc-AdenoCA	2/229	1
Prost-AdenoCA	2/178	1
Bladder-TCC	0/23	0
Breast-DCIS	0/3	0
Breast-LobularCA	0/13	0
Cervix-AdenoCA	0/2	0
Cervix-SCC	0/18	0
CNS-PiloAstro	0/89	0
Head-SCC	0/56	0
Lung-AdenoCA	0/37	0
Lung-SCC	0/47	0
Myeloid-AML	0/8	0
Stomach-AdenoCA	0/68	0
Thy-AdenoCA	0/48	0

Supplementary Table 3: Feature importance in random forest classifier trained on ATRX/DAXX^{trunc} and TERT^{mod} tumor samples.

Feature	Importance
TTTGGG singleton divergence to expected count	13.59
TTCGGG singleton divergence to expected count	11.92
breakpoint count	11.01
telomere insertion count	10.03
telomere content tumor/control log2 ratio	5.34
TGAGGG singleton divergence to expected count	5.02
TCAGGG singleton divergence to expected count	3.25
TTGGGG singleton divergence to expected count	2.83

Supplementary Table 4: Histology overview. Information on the tumor types included in this study.

Abbreviation	Organ	Included subtypes
Biliary-AdenoCA	Biliary	Cholangiocarcinoma; Cholangiocarcinoma, papillary
Bladder-TCC	Bladder	Transitional cell carcinoma; Transitional cell carcinoma, papillary
Bone-Benign	Bone/SoftTissue	Osteoblastoma; Osteofibrous dysplasia; Chondroblastoma; Chrondromyxoid fibroma
Bone-Epith	Bone/SoftTissue	Adamantinoma; Chordoma
Bone-Osteosarc	Bone/SoftTissue	Osteosarcoma
Breast-AdenoCA	Breast	Infiltrating duct carcinoma; Intraductal papillary adenocarcinoma with invasion; Medullary carcinonoma; Mucinous adenocarcinoma
Breast-DCIS	Breast	Duct micropapillary carcinoma
Breast-LobularCA	Breast	Lobular carcinoma
Cervix-AdenoCA	Cervix	Adenocarcinoma
Cervix-SCC	Cervix	Squamous Cell Carcinoma
CNS-GBM	CNS	Glioblastoma
CNS-LGG	CNS	Oligodendroglioma; ATRX-mutant, 1p/19q-intact lower grade gliomas
CNS-Medullo	CNS	Desmoplastic medulloblastoma; Large cell medulloblastoma; Medulloblastoma
CNS-PiloAstro	CNS	Pilocytic astrocytoma
ColoRect-AdenoCA	Colon/Rectum	Adenocarcinoma; Adenocarcinoma, mucinous; Mucinous adenocarcinoma
Eso-AdenoCA	Esophagus	Adenocarcinoma
Head-SCC	Head/Neck	Squamous cell carcinoma
Kidney-ChRCC	Kidney	Adenocarcinoma, chromophobe type
Kidney-RCC	Kidney	Adenocarcinoma, clear cell type; Adenocarcinoma, papillary type
Liver-HCC	Liver	Combined hepatocellular + cholangiocarcinoma; Fibrolamellar hepatocellular carcinoma; Hepatocellular carcinoma
Lung-AdenoCA	Lung	Adenocarcinoma, in situ; Adenocarcinoma, invasive; Adenocarcinoma, invasive, mucinous
Lung-SCC	Lung	Basaloid squamous cell carcinoma; Squamous cell carcinoma
Lymph-BNHL	Lymphoid	Burkitt lymphoma; Diffuse large B-cell lymphoma; Follicular lymphoma; Marginal zone B-cell lymphoma; Post-transplant lymphoproliferative disorder, early lesion
Lymph-CLL	Lymphoid	Chronic lymphocytic leukemia
Myeloid-AML	Myeloid	Acute myeloid leukemia
Ovary-AdenoCA	Ovary	Adenocarcinoma; Serous cystadenocarcinoma
Panc-AdenoCA	Pancreas	Acinar cell carcinoma; Adenocarcinoma; Adenocarcinoma, mucinous; Carcinoma, adenosquamous; Invasive carcinoma arising in IPMN; Pancreatic ductal carcinoma
Panc-Endocrine	Pancreas	Neuroendocrine carcinoma
Prost-AdenoCA	Prostate	Adenocarcinoma
Skin-Melanoma	Skin	Malignant melanoma
SoftTissue-Leiomyo	Bone/SoftTissue	Leiomyosarcoma
SoftTissue-Liposarc	Bone/SoftTissue	Liposarcoma
Stomach-AdenoCA	Stomach	Adenocarcinoma; Adenocarcinoma, mucinous; Adenocarcinoma, papillary; Adenocarcinoma, poorly cohesive; Adenocarcinoma, tubular
Thy-AdenoCA	Thyroid	Adenocarcinoma, classical type; Adenocarcinoma, columnar cell type; Adenocarcinoma, follicular type
Uterus-AdenoCA	Uterus	Adenocarcinoma, endometrioid; Serous cystadenocarcinoma

Supplementary References

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Supplementary Information:

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Mitochondrial variants and HLA/immunogenicity

Peter J Campbell[1,2], Yiwen Chen[148], Chad J Creighton[241], Li Ding[138,139,146], Akihiro Fujimoto[48], Masashi Fujita[48], Gad Getz[3,4,5,6], Leng Han[231], Takanori Hasegawa[87], Shuto Hayashi[87], Seiya Imoto[86,87], Young Seok Ju[2,181], Hyung-Lae Kim[27], Youngwook Kim[96,97], Youngil Koh[307,308], Mitsuhiro Komura[87], Jun Li[148], **Han Liang**#[397], Iñigo Martincorena[2], Satoru Miyano[87], Shinichi Mizuno[398], **Hidewaki Nakagawa**#[48], Keunchil Park[206,207], Eigo Shimizu[87], Yumeng Wang[148,399], John N Weinstein[395,396], Yanxun Xu[400], Rui Yamaguchi[87], Fan Yang[384], Yang Yang[231], Christopher J Yoon[181], Sung-Soo Yoon[308], Yuan Yuan[148], Fan Zhang[246] and Zemin Zhang[246,271]

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Malik Alawi[401,402], Ivan Borozan[9], Daniel S Brewer[403,404], Colin S Cooper[404,405,406], Nikita Desai[45], **Roland Eils**#[52,54,66,67], Vincent Ferretti[45,69], Adam Grundhoff[401,407], Murat Iskar[408], Kortine Kleinheinz[52,54], Peter Lichter[408], **Hidewaki Nakagawa**#[48], Akinyemi I Ojesina[255,256,257], Chandra Sekhar Pedamallu[3,6,172], Matthias Schlesner[52,110], Xiaoping Su[144] and Marc Zapatka[408]

Tumour Specific Providers – Australia (Ovarian cancer)

Kathryn Alsop[409,410], Australian Ovarian Cancer Study Group[187,311,411], **David D L Bowtell#**[187,291], Timothy JC Bruxner[185], Angelika N Christ[185], Elizabeth L Christie[187], Stephen M Cordner[412], Prue A Cowin[187], Ronny Drapkin[413], Dariush Etemadmoghadam[187,188], Sian Fereday[414], Dale W Garsed[187,188], Joshy George[170], Sean M Grimmond[363], Anne Hamilton[187], Oliver Holmes[311,312], Jillian A Hung[415,416], Karin S Kassahn[185,417], Stephen H Kazakoff[311,312], Catherine J Kennedy[418,419], Conrad R Leonard[311,312], Linda Mileshkin[187], David K Miller[185,360,420], Gisela Mir Arnau[187], Chris Mitchell[187], Felicity Newell[311,312], Katia Nones[311,312], Ann-Marie Patch[311,312], John V Pearson[311,312], Michael C Quinn[311,312], Mark Shackleton[188,218], Darrin F Taylor[185], Heather Thorne[187], Nadia Traficante[187], Ravikiran Vedururu[187], Nick M Waddell[312], Nicola Waddell[311,312], Paul M Waring[253], Scott Wood[311,312], Qinying Xu[311,312] and Anna deFazio[421,422,423]

Tumour Specific Providers – Australia (Pancreatic cancer)

Matthew J Anderson[185], Davide Antonello[424], Andrew P Barbour[425,426], Claudio Bassi[424], Samantha Bersani[427], **Andrew V Biankin#**[359,360,361,362], Timothy JC Bruxner[185], Ivana Cataldo[427,428], David K Chang[360,362], Lorraine A Chantrill[360], Yoke-Eng Chiew[421], Angela Chou[360,429], Angelika N Christ[185], Sara Cingarlini[37], Nicole Cloonan[430], Vincenzo Corbo[428,431], [432], Fraser R Duthie[433,434], J Lynn Fink[105,185], Anthony J Gill[360,435], Janet S Graham[362,436], **Sean M Grimmond#**[363], Ivon Harliwong[185], Oliver Holmes[311,312], Nigel B Jamieson[361,362,437], Amber L Johns[360,420], Karin S Kassahn[185,417], Stephen H Kazakoff[311,312], James G Kench[360,435,438], Luca Landoni[424], Rita T Lawlor[428], Conrad R Leonard[311,312], Andrea Mafficini[428], Neil D Merrett[424,439], David K Miller[185,360,420], Marco Miotto[424], Elizabeth A Musgrove[362], Adnan M Nagrial[360], Felicity Newell[311,312], Katia Nones[311,312], Karin A Oien[253,440], Marina Pajic[360], Ann-Marie Patch[311,312], John V Pearson[311,312], Mark Pinese[360], Andreia V Pinho[360], Michael C Quinn[311,312], Alan J Robertson[185], Ilse Rooman[360], Borislav C Rusev[428], Jaswinder S Samra[424,435], Maria Scardoni[427], Christopher J Scarlett[360,441], Aldo Scarpa[428], Elisabetta Sereni[424], Katarzyna O Sikora[428], Michele Simbolo[431], Morgan L Taschuk[45], Christopher W Toon[360], Giampaolo Tortora[37,38], Caterina Vicentini[428], Nick M Waddell[312], Nicola Waddell[311,312], Scott Wood[311,312], Jianmin Wu[360], Qinying Xu[311,312] and Nikolajs Zeps[442]

Tumour Specific Providers – Australia (Skin cancer)

Lauri A Aaltonen[443], Andreas Behren[444], Hazel Burke[445], Jonathan Cebon[444], Rebecca A Dagg[446], Ricardo De Paoli-Iseppi[447], Ken Dutton-Regester[311], Matthew A Field[448], Anna Fitzgerald[449], Sean M Grimmond[363], **Nicholas K Hayward#**[311,445], Peter Hersey[445], Oliver Holmes[311,312], Valerie Jakrot[445], Peter A Johansson[311], Hojabr Kakavand[447], Stephen H Kazakoff[311,312], Richard F Kefford[450], Loretta MS Lau[451], Conrad R Leonard[311,312], Georgina V Long[452], **Graham J Mann#**[453,454], Felicity Newell[311,312], Katia Nones[311,312], Ann-Marie Patch[311,312], John V Pearson[311,312], Hilda A Pickett[451], Antonia L Pritchard[311], Gulietta M Pupo[455], Robyn PM Saw[452],

Sarah-Jane Schramm[456], **Richard A Scolyer#**[422,452,457,458], Mark Shackleton[188,218], Catherine A Shang[459], Ping Shang[452], Andrew J Spillane[452], Jonathan R Stretch[452], Varsha Tembe[456], John F Thompson[452], Ricardo E Vilain[457], Nick M Waddell[312], Nicola Waddell[311,312], James S Wilmott[452], Scott Wood[311,312], Qinying Xu[311,312] and Jean Y Yang[460]

Tumour Specific Providers – Canada (Pancreatic cancer)

John Bartlett[461,462], Prashant Bavi[463], Ivan Borozan[9], Dianne E Chadwick[464], Michelle Chan-Seng-Yue[463], Sean Cleary[463,465], Ashton A Connor[466,467], Karolina Czajka[468], Robert E Denroche[463], Neesha C Dhani[469], Jenna Eagles[79], Vincent Ferretti[45,69], Steven Gallinger[463,466,467], Robert C Grant[463,470], David Hedley[469], Michael A Hollingsworth[471], **Thomas J Hudson#**[78,79], Gun Ho Jang[463], Jeremy Johns[79], Sangeetha Kalimuthu[463], Sheng-Ben Liang[472], Ilinca Lungu[463,473], Xuemei Luo[9], Faridah Mbabaali[79], **John D McPherson#**[79,463,474], Treasa A McPherson[470], Jessica K Miller[79], Malcolm J Moore[469], Faiyaz Notta[463,475], Danielle Pasternack[79], Gloria M Petersen[476], Michael H A Roehrl[133,463,477,478,479], Michelle Sam[79], Iris Selander[470], Stefano Serra[253], Sagedeh Shahabi[472], **Lincoln D Stein#**[9,10], Morgan L Taschuk[45], Sarah P Thayer[106], Lee E Timms[79], Gavin W Wilson[9,463], Julie M Wilson[463] and Bradly G Wouters[480]

Tumour Specific Providers – Canada (Prostate cancer)

Timothy A Beck[45], Vinayak Bhandari[9], Paul C Boutros[9,133,142,143], **Robert G Bristow#**[133,481,482,483,484], Colin C Collins[151], Shadrielle MG Espiritu[9], Neil E Fleshner[485], Natalie S Fox[9], Michael Fraser[9], Syed Haider[9], Lawrence E Heisler[486], Vincent Huang[9], Emilie Lalonde[9], Julie Livingstone[9], John D McPherson[79,463,474], Alice Meng[487], Veronica Y Sabelnykova[9], Adriana Salcedo[9], Yu-Jia Shiah[9], Theodorus Van der Kwast[488] and Takafumi N Yamaguchi[9]

Tumour Specific Providers – China (Gastric cancer)

Shuai Ding[489], Daiming Fan[490], Yong Hou[39,249], Yi Huang[153,154], Lin Li[39], Siliang Li[39,249], Dongbing Liu[39,249], Xingmin Liu[39,249], **Youyong Lu#**[28,29,30], Yongzhan Nie[490,491], Hong Su[39,249], Jian Wang[39], Kui Wu[39,249], Xiao Xiao[154], Rui Xing[29,492], **Huanming Yang#**[39], Shanlin Yang[489], Yingyan Yu[493], [230], Xiuqing Zhang[39], Yong Zhou[39] and Shida Zhu[39,249]

Tumour Specific Providers – EU: France (Renal cancer)

Rosamonde E Banks[494], Guillaume Bourque[495,496], Alvis Brazma[7], Paul Brennan[497], **Mark Lathrop#**[496], Louis Letourneau[498], Yasser Riazalhosseini[496], Ghislaine Scelo[497], **Jörg Tost#**[499], Naveen Vasudev[500] and Juris Viksna[501]

Tumour Specific Providers – EU: United Kingdom (Breast cancer)

Sung-Min Ahn[502], Ludmil B Alexandrov[2,317], Samuel Aparicio[503], Laurent Arnould[504], MR Aure[505], Shriram G Bhosle[2], E Birney[7], Ake Borg[506], S Boyault[507], AB Brinkman[508], JE Brock[509], A Broeks[510], Adam P Butler[2], AL Børresen-Dale[505], C Caldas[511,512], Peter J Campbell[1,2], Suet-Feung Chin[511,512], Helen Davies[2], C Desmedt[513], L Dirix[514], S Dronov[2], Anna Ehinger[515], JE Eyfjord[516], GG Van den Eynden[517], A Fatima[217], Jorge Reis Filho[518], JA Foekens[519], PA Futreal[520], Øystein Garred[521,522], Moritz Gerstung[7,8], Dilip D Giri[518], D Glodzik[2], Dorthe Grabau[523], Holmfridur Hilmarsdottir[516], GK Hooijer[524], Jocelyne Jacquemier[525], SJ Jang[526], Jon G Jonasson[516], Jos Jonkers[527], HY Kim[525], Tari A King[528,529], Stian Knappskog[2], G Kong[525], S Krishnamurthy[530], S Van Laere[514], SR Lakhani[531], A Langerød[505], Denis Larsimont[532], HJ Lee[526], JY Lee[533], Ming Ta Michael Lee[520], Yilong Li[2], Ole Christian Lingjærde[534], Gaetan MacGrogan[535], JW Martens[536], Sancha Martin[2,369], Iñigo Martincorena[2], Andrew Menzies[2], Sandro Morganella[2], Ville Mustonen[320,321,322], Serena Nik-Zainal[2,324,325,326], Sarah O'Meara[2], I Pauporté[18], Sarah Pinder[537], X Pivot[538], Elena Provenzano[539], CA Purdie[540], Keiran M Raine[2], M Ramakrishna[2], K Ramakrishnan[2], AL Richardson[217], M Ringnér[506], Javier Bartolomé Rodriguez[105], FG Rodríguez-González[175], G Romieu[541], Roberto Salgado[253], Torill Sauer[534], R Shepherd[2], AM Sieuwerts[177], PT Simpson[531], M Smid[542], C Sotiriou[55], PN Span[543], J Staaf[506], Lucy Stebbings[2], Ólafur Andri Stefánsson[544], Alasdair Stenhouse[545], **Michael Rudolf Stratton**#[2], HG Stunnenberg[249,546], Fred Sweep[547], BK Tan[548], Jon W Teague[2], Gilles Thomas[549], AM Thompson[545], S Tommasi[550], I Treilleux[551,552], Andrew Tutt[217], NT Ueno[393], Peter Van Loo[63,64], P Vermeulen[514], Alain Viari[428], MJ van de Vijver[253], A Vincent-Salomon[546], David C Wedge[2,354,355], Bernice Huimin Wong[553], Lucy Yates[2], X Zou[2], CHM van Deurzen[536] and L van't Veer[554,555]

Tumour Specific Providers – Germany (Malignant lymphoma)

Ole Ammerpohl[556,557], Sietse Aukema[558,559], Anke K Bergmann[560], Stephan H Bernhart[276,277,281], Hans Binder[276,277], Arndt Borkhardt[561], Christoph Borst[562], Benedikt Brors[82,119,278], Birgit Burkhardt[563], Alexander Claviez[564], Roland Eils[52,54,66,67], Maria Elisabeth Goebler[565], Andrea Haake[556], Siegfried Haas[562], Martin Hansmann[566], Jessica I Hoell[561], Steve Hoffmann[277,279,280,281], Michael Hummel[567], Daniel Hübschmann[54,66,83,84,85], Dennis Karsch[568], Wolfram Klapper[559], Kortine Kleinheinz[52,54], Michael Kneba[568], Jan O Korbel[7,8], Helene Kretzmer[277,281], Markus Kreuz[569], Dieter Kube[570], Ralf Küppers[571], Chris Lawerenz[67], Dido Lenze[567], Peter Lichter[408], Markus Loeffler[569], Cristina López[262,556], Luisa Mantovani-Löffler[572], Peter Möller[573], German Ott[574], Bernhard Radlwimmer[408], Julia Richter[556,559], Marius Rohde[575], Philip C Rosenstiel[576], Andreas Rosenwald[577], Markus B Schilhabel[576], Matthias Schlesner[52,110], Stefan Schreiber[578], **Reiner Siebert**#[261,262], Peter F Stadler[276,277,281], Peter Staib[579], Stephan Stilgenbauer[580], Stephanie Sungalee[8], Monika Szczepanowski[559], Umut H Toprak[54,581], Lorenz HP Trümper[570], Rabea Wagener[262,556] and Thorsten Zenz[82]

Tumour Specific Providers – Germany (Pediatric Brain cancer)

Ivo Buchhalter[52,53,54], Juergen Eils[66,67], Roland Eils[52,54,66,67], Volker Hovestadt[408], Barbara Hutter[80,81,82], David TW Jones[301,302], Natalie Jäger[52], Christof von Kalle[84], Marcel Kool[98,301], Jan O Korbel[7,8], Andrey Korshunov[98], Pablo Landgraf[582], Chris Lawerenz[67], Hans Lehrach[583], **Peter Lichter**#[408], Paul A Northcott[584], Stefan M Pfister[98,301,585], Bernhard Radlwimmer[408], Guido Reifenberger[582], Matthias Schlesner[52,110], Hans-Jörg Warnatz[583], Joachim Weischenfeldt[8,113,114], Stephan Wolf[586], Marie-Laure Yaspo[583] and Marc Zapatka[408]

Tumour Specific Providers – Germany (Prostate cancer)

Yassen Assenov[587], Benedikt Brors[82,119,278], Juergen Eils[66,67], Roland Eils[52,54,66,67], Lars Feuerbach[119], Clarissa Gerhauser[285], Jan O Korbel[7,8], Chris Lawerenz[67], Hans Lehrach[583], Sarah Minner[588], Christoph Plass[285], **Guido Sauter**#[589], Thorsten Schlomm[114,590], Nikos Sidiropoulos[113], Ronald Simon[589], **Holger Sültmann**#[82,591], Hans-Jörg Warnatz[583], Dieter Weichenhan[285], Joachim Weischenfeldt[8,113,114] and Marie-Laure Yaspo[583]

Tumour Specific Providers – India (Oral cancer)

Nidhan K Biswas[592], Luca Landoni[424], Arindam Maitra[592], **Partha P Majumder**#[592] and **Rajiv Sarin**#[593]

Tumour Specific Providers – Italy (Pancreatic cancer)

Davide Antonello[424], Stefano Barbi[431], Claudio Bassi[424], Samantha Bersani[427], Giada Bonizzato[428], Cinzia Cantù[428], Ivana Cataldo[427,428], Sara Cingarlini[37], Vincenzo Corbo[428,431], [432], Angelo P Dei Tos[594], Matteo Fassan[595], Sonia Grimaldi[428], Luca Landoni[424], Rita T Lawlor[428], Claudio Luchini[427], Andrea Mafficini[428], Giuseppe Malleo[424], Giovanni Marchegiani[424], Michele Milella[37], Marco Miotto[424], Salvatore Paiella[424], Antonio Pea[424], Paolo Pederzoli[424], Borislav C Rusev[428], Andrea Ruzzenente[424], Roberto Salvia[424], Maria Scardoni[427], **Aldo Scarpa**#[428], Elisabetta Sereni[424], Michele Simbolo[431], Nicola Sperandio[428], Giampaolo Tortora[37,38] and Caterina Vicentini[428]

Tumour Specific Providers – Japan (Biliary tract cancer)

Yasuhito Arai[33], Natsuko Hama[33], Nobuyoshi Hiraoka[596], Fumie Hosoda[33,597], Mamoru Kato[366], Hiromi Nakamura[33], Hidenori Ojima[598], Takuji Okusaka[599], **Tatsuhiro Shibata**#[33,34], Yasushi Totoki[33] and Tomoko Urushidate[34]

Tumour Specific Providers – Japan (Gastric cancer)

Hiroyuki Aburatani#[272], Yasuhito Arai[33], Masashi Fukayama[600], Natsuko Hama[33], Fumie Hosoda[33,597], Shumpei Ishikawa[601], Hitoshi Katai[602], Mamoru Kato[366], Hiroto Katoh[603], Daisuke Komura[601], Genta Nagae[272,284], Hiromi Nakamura[33], Hirofumi Rokutan[604], Mihoko Saito-Adachi[33], **Tatsuhiro Shibata#**[33,34], Akihiro Suzuki[272,605], Hirokazu Taniguchi[606], Kenji Tatsuno[272], Yasushi Totoki[33], Tetsuo Ushiku[600], Shinichi Yachida[33,607] and Shogo Yamamoto[272]

Tumour Specific Providers – Japan (Liver cancer)

Hiroyuki Aburatani[272], Hiroshi Aikata[608], Koji Arihiro[608], Shun-ichi Ariizumi[609], Keith A Boroevich[47,48], Kazuaki Chayama[608], Akihiro Fujimoto[48], Masashi Fujita[48], Mayuko Furuta[48], Kunihito Gotoh[610], Natsuko Hama[33], Takanori Hasegawa[87], Shinya Hayami[611], Shuto Hayashi[87], Satoshi Hirano[612], Seiya Imoto[86,87], Mamoru Kato[366], Yoshiiku Kawakami[608], Kazuhiro Maejima[48], Satoru Miyano[87], Genta Nagae[272,284], **Hidewaki Nakagawa#**[48], Hiromi Nakamura[33], Toru Nakamura[612], Kaoru Nakano[48], Hideki Ohdan[608], Aya Sasaki-Oku[48], **Tatsuhiro Shibata#**[33,34], Yuichi Shiraishi[87], Hiroko Tanaka[87], Yasushi Totoki[33], Tatsuhiko Tsunoda[47,220,221,222], Masaki Ueno[611], Rui Yamaguchi[87], Masakazu Yamamoto[609] and Hiroki Yamaue[611]

Tumour Specific Providers – Singapore (Biliary tract cancer)

Su Pin Choo[613], Ioana Cutcutache[267,319], Narong Khuntikeo[424,614], John R McPherson[267,319], Choon Kiat Ong[615], Chawalit Pairojkul[253], Irinel Popescu[616], **Steven G Rozen#**[267,268,319], **Patrick Tan#**[254,266,267,268] and **Bin Tean Teh#**[266,267,268,269,270]

Tumour Specific Providers – South Korea (Blood cancer)

Keun Soo Ahn[617], Hyung-Lae Kim[27], Youngil Koh[307,308] and **Sung-Soo Yoon#**[308]

Tumour Specific Providers – Spain (Chronic Lymphocytic Leukemia)

Marta Aymerich[618], **Elias Campo#**[619,620], Josep Ll Gelpi[46,71], Ivo G Gut[135,136], Marta Gut[135,136], Armando Lopez-Guillermo[621], Carlos López-Otín[622], Xose S Puente[623], Romina Royo[105] and David Torrents[105,111]

Tumour Specific Providers – United Kingdom (Bone cancer)

Fernanda Amary[624], Daniel Baumhoer[625], Sam Behjati[2], Bodil Bjerkehagen[626], **Peter J Campbell#**[1,2], **Adrienne M Flanagan#**[627], PA Futreal[520], Ola Myklebost[628], Nischalan Pillay[629], Patrick Tarpey[630], Roberto Tirabosco[631] and Olga Zaikova[632]

Tumour Specific Providers – United Kingdom (Chronic myeloid disorders)

Jacqueline Boultwood[633], David T Bowen[2], Adam P Butler[2], **Peter J Campbell#**[1,2], Mario Cazzola[634], Carlo Gambacorti-Passerini[186], Anthony R Green[295], Eva Hellstrom-Lindberg[635], Luca Malcovati[634], Sancha Martin[2,369], Jyoti Nangalia[636], Elli Papaemmanuil[2] and Paresh Vyas[311,637]

Tumour Specific Providers – United Kingdom (Esophageal cancer)

Yeng Ang[638], Hugh Barr[639], Duncan Beardsmore[640], Matthew Eldridge[294], **Rebecca C Fitzgerald#**[325], James Gossage[641], Nicola Grehan[325], George B Hanna[642], Stephen J Hayes[643,644], Ted R Hupp[645], David Khoo[646], Jesper Lagergren[635,647], Laurence E Lovat[251], Shona MacRae[395], Maria O'Donovan[325], J Robert O'Neill[648], Simon L Parsons[649], Shaun R Preston[650], Sonia Puig[651], Tom Roques[652], Grant Sanders[248], Sharmila Sothi[653], Simon Tavaré[294], Olga Tucker[654], Richard Turkington[655], Timothy J Underwood[656] and Ian Welch[657]

Tumour Specific Providers – United Kingdom (Prostate cancer)

Nicholas Van As[658], Daniel M Berney[659], Johann S De Bono[405], G Steven Bova[330], Daniel S Brewer[403,404], Adam P Butler[2], Declan Cahill[658], Niedzica Camacho[405], **Colin S Cooper#**[404,405,406], Nening M Dennis[658], Tim Dudderidge[658], Sandra E Edwards[405], **Rosalind A Eeles#**[405,658], Cyril Fisher[658], Christopher S Foster[660,661], Mohammed Ghori[2], Pelvender Gill[637], Vincent J Gnanapragasam[383,662], Gunes Gundem[2], Freddie C Hamdy[663], Steve Hawkins[294], Steven Hazell[658], William Howat[383], William B Isaacs[292], Katalin Karaszi[637], Jonathan D Kay[251], Vincent Khoo[658], Zsofia Kote-Jarai[405], Barbara Kremeyer[2], Pardeep Kumar[658], Adam Lambert[637], Daniel A Leongamornlert[2,405], Naomi Livni[658], Hayley J Luxton[251], Andy G Lynch[294,295,310], Luke Marsden[637], Charlie E Massie[294], Lucy Matthews[405], Erik Mayer[658,664], Ultan McDermott[2], Sue Merson[405], Thomas J Mitchell[2,295,383], David E Neal[294,383], Anthony Ng[665], David Nicol[658], Christopher Ogden[658], Edward W Rowe[658], Nimish C Shah[383], Jon W Teague[2], Sarah Thomas[658], Alan Thompson[658], Peter Van Loo[63,64], Clare Verrill[637,666], Tapio Visakorpi[330], Anne Y Warren[383,667], David C Wedge[2,354,355], Hayley C Whitaker[251], Yong-Jie Yu[659], Yongwei Yu[230], Jorge Zamora[2,287,288,289] and Hongwei Zhang[230]

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